DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/9/2009 has been entered.

Receipt is acknowledged of applicant's Amendment/Remarks filed 9/9/2009. Claims 77 and 94 have been amended. Claims 1-76, 81, and 99-106 are cancelled. Thus, claims 77-80 and 82-98 are pending and currently under consideration.

Information Disclosure Statement

2. The information disclosure statement (IDS) filed on 2/20/2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered.

Response to Arguments

3. Applicant's arguments filed 9/92009 have been fully considered but they are not persuasive.

Applicant argues that there is no drying between forming the sterile suspension (ii) and storing the pharmaceutical composition of (vi), and that if the suspension was dried and re-suspended, it would inherently no longer be the suspension of the appropriate preceding step. In response it is respectfully submitted that step (iv) states that all or part of the solvent is partially removed. Thus, the claims as best understood (see 112, 2nd paragraph rejection *infra*) include methods in which all the solvent is removed after water is added. Thus, the steps of removing the solvent (i.e. acetone and water) by filtration and drying are not precluded by the claim language. In addition, the term "comprising" is interpreted as broad and open, and thus the isolation steps taught by Harris et al. are not excluded by the claim language. Furthermore, the isolation of the product before steps (v)-(vii) is not deemed as essential because it does not materially affect the end product.

The Applicant further argues that it would be clear to a person of skill in the art to produce a sterile *dry* product from the teachings of Harris et al. because this is subsequently used in various sterile mometasone furoate monohydrate compositions. Applicant further argues that that the claimed one-step process is not obvious over the two-step process taught by Harris et al. (i.e. examples 1-2) , which includes an isolation step, and that Harris et al. does not provide a reason why one of ordinary skill in the art would omit the drying step of example 1. In response, it is respectfully submitted that the isolation of the steroid is a design choice and not an essential step because it does not materially affect the end product. Solid products are often isolated because they are easier to transport than the suspended products. However, when the solid product is to

be immediately processed into the final suspended product for use in a nebulizer, it would be obvious to the ordinary artisan to leave the steroid product in the water-based suspension for the further processing steps.

The Applicant further argues that if the mometasone furoate monohydrate were to remain is suspension, there would be a number of problems including (i) the presence of acetone in the suspension and (ii) the mometasone furoate monohydrate would be in a dilute suspension comprising a large amount of water making it difficult to calculate the precise amount of mometasone furoate monohydrate present or to remove a precise amount of mometasone furoate monohydrate from the suspension. Applicant asserts that a significant number of complex changes would be required to address these issues and convert the two stage method of Harris et al. into the single stage method of the instant claims. In response it is respectfully submitted that the solvent removal (step (iii) in the instant claims) is optional, and thus the presence of acetone is not precluded by the claim language. Further, in response to Applicant's argument that it would be difficult to calculate the precise amount of mometasone furoate monohydrate present in the suspension, it is noted that amounts are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, the "complex changes" the Applicant refers to are not deemed necessary, as the changes would not result in meeting claimed limitations.

Thus, for these reasons, Applicant's arguments are found unpersuasive. Said rejection is maintained.

REJECTIONS

4. The following rejections and/or objections are either reiterated from the 1/9/2009 Office Action or newly applied. They constitute the complete set of rejections and/or objections presently being applied in the instant application.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77-80 and 82-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 77 and 94 recitation of "optionally removing all or part of the solvent from the suspension of (iii)" following by "treating the sterile suspension of (iii) or (iv)" is indefinite because it is unclear how the steroid is still in suspension if the all of the solvent is removed. A solvent is broadly is interpreted as any substance that dissolves or can dissolve. Thus, water is included by the term "solvent." If all the solvent of step (i) and all of the water of step (iii) is removed, then the steroid is no longer in suspension.

Claims 78-80, 82-93, and 95-98 are rejected for being dependent on a rejected base claim. For examination purposes and in the interest of compact prosecution, it will be assumed that if all of the solvent is removed in step (iv), the steroid is re-suspended in sterile water.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 77-80, and 82-98 rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al. (US 6,187,765 B1).

The instant claims are directed to methods for preparing sterile pharmaceutical compositions of the steroid, budesonide, comprising dissolving the non-sterile steroid in a solvent to yield a solution of the steroid; filtering the solution to yield a sterile solution; combining the sterile solution with sterile water to form a suspension; optionally removing all or part of the solvent; treating the suspension to obtain a particle size distribution having a mass median diameter less than 10 μm; under sterile conditions combining said suspension with a pharmaceutically acceptable carrier to yield a sterile composition; and storing said composition in a sterile container.

Harris et al. teaches aqueous suspensions of water-insoluble pharmaceutical substance intended for inhalation therapy (see column 1, lines 12-15). Harris further teaches in Example 1, a method of preparing a sterile suspension of a steroid, mometasone furoate, comprising dissolving said steroid in acetone, a class 3 solvent as claimed in the instant claim 83; filtering said solution through a sterilizing filter, such as a filtration medium having pore sizes not exceeding 0.2 μm in diameter, as claimed in the instant claims 89 and 96, into a sterile vessel; heating said sterile solution to about 45-50 °C and slowly adding sterile purified water over 15 min.; while maintaining the temperature and more of the sterile water and stir for 30 min.; continuing to maintain the

temperature and stir for another 30 min. during which a precipitate forms; slowly adding more water and stirring for 60 min. at the elevated temperature; stirring at 60 min. at the elevated temperature; cooling the mixture to ambient temperature while stirring; filtering said precipitate and washing with water; and drying under vacuum to yield dry sterile mometasone furoate (see column 6, lines 25-62). The sterile mometasone furoate is then added to a sterile carrier solution comprising polysorbate (a surfactant) as claimed in the instant claim 90, to form a suspension; said suspension is passed through a Microfluidizer to yield a suspension with a median particle size of 1.24 as claimed in the instant claims 91 and 97 (see column 7, lines 65-68); and the sterile suspension is transferred to sterile containers for use in a nebulizer (i.e. an ampoule as claimed in the instant claim 93) (see column 6, line 64 to column 7, line 36).

Harris et al. do not teach a method wherein the steroid says in suspension after the solvent is removed. However, the claims as best understood (see 112, 2nd paragraph rejection *supra*) include methods in which all the solvent is removed after water is added. Thus, the steps of removing the solvent by filtration and drying are not precluded by the claim language. In addition, the term "comprising" is interpreted as broad and open, and thus the isolation steps taught by Harris et al. are not excluded by the claim language. Furthermore, the isolation of the product is not deemed as essential because it does not materially affect the end product.

Harris et al. does not teach a method of preparing a sterile suspension of steroid where the steps are in the same order as claimed. Specifically, Harris et al. teaches the sterile suspension is combined with a carrier before the suspension is treated to obtain

the desired particle size, whereas the carrier is added after the sterile suspension is treated to obtain the desired particle size in the instant claims. However, it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. *Ex Parte Rubin*, 128 USPQ 440 (Bd. App. 1959). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). Thus, adding the carrier after the suspension is treated to obtain the desired particle size instead of before is deemed as an obvious modification absence evidence to the contrary.

Harris et al. also does not teach a method for preparing a sterile suspension of steroid wherein the steroid is budesonide. However, Harris et al. does teach that aqueous suspensions of drug particles for nebulization are known, and mentions budesonide as a commercially available product (see column 2, lines 5-12). Harris et al. also teaches that formulations that are to be inhaled must be free of pathogenic organisms, and thus be prepared and handled under sterile conditions (see column 3, lines 7-10).

It would have been obvious to one of ordinary skill in the art to substitute budesonide for mometasone furoate as the steroid in the method taught by Harris et al., to produce a sterile suspension of budesonide. One of ordinary skill in the art would have been motivated to do so in order to produce an inhalable formulation of budesonide free of any potential pathogenic organisms. One of ordinary skill in the art would have had a reasonable expectation of success in producing a sterile suspension

of budesonide because Harris et al. teach a method of producing aqueous suspensions for inhalation of the corticosteroid mometasone furoate.

In regards to the instant claims 78-79, wherein the budesonide steroid is a powder or micronized power, Harris et al. does not explicitly teach using a powder steroid, or a micronized powder sterile to prepare the sterile suspensions. However, it would have been obvious to one of ordinary skill in the art at the time of invention to use a powder or micronized powder of the steroid to prepare the sterile suspensions because powders and micronized powders have an increase surface area. One of ordinary skill in the art would have been motivated to increase the surface area of the steroid to increase the rate at which the steroid dissolves in the solvent.

In regards to claims 82, 84, and 95, Harris et al. does not teach dissolving the steroid in alcohol or a class 2 solvent. Harris et al. teaches dissolving the steroid in acetone (as described *supra*). However, it is been held that the selection of a known material based on its suitability for its intended use supported a *prima facie* case of obviousness determination in *Sinclair & Carroll Co. V. Interchemical Corp.*, 325, US 327, 65 USPQ 297 (1945). Accordingly, since alcohol and class 2 solvents are known solvents, it would have been obvious to one or ordinary skill in the art at the time of the invention to select an appropriate solvent to dissolve the steroid.

In regards to the instant claim 85-86, the boiling point of acetone is 56.5°C. Harris et al. teaches dissolving the steroid at 45-50°C which is significantly overlaps with the range as claimed in the instant claim 85. Harris et al. does not teach adding the steroid to the solvent wherein the solvent is at reflux. However, it would have been

obvious to one of ordinary skill in the art at the time of the invention to add the steroid to the solvent at reflux. One of ordinary skill in the art would have been motivated to do so to increase the rate at which the steroid dissolves in said solvent.

In regards to claims 87, Harris et al. does not teach removing the solvent under reduced pressure. Acetone (the solvent taught by Harris et al.) will evaporate on its own at room temperature to a certain extent. Heating any solvent or reducing the pressure any solvent is kept at, will increases the rate at which the solvent evaporates. Harris et al. heats the acetone (see column 6, lines 37-40). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to remove the solvent under reduce pressure. One of ordinary skill in the art would have been motivated to do so to increase the rate of solvent removal.

In regards to the instant claims 92 and 98, Harris et al. does not explicitly teach steroid particles in the suspension having a mass median diameter in the range of 2-3 µm. However, Harris et al. does teach that the preferred average particle size for inhaled particles is 0.5 to 5 µm (see column 1, lines 27-43 and column 2, lines 65-67). Furthermore, Harris et al. claims suspensions where the particle size is less than 5 µm, which significantly overlaps with range as claimed (see column 10, claim 14), and teaches suspensions where the median particle size is 1.24 µm. In this case, where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 UPSQ 90 (CCPA 1976). Furthermore, while the references do not explicitly teach the claimed particle size range, it is the Examiner's opinion that the determination of optimal or workable particle size

range by routine experimentation is obvious absent showing of criticality of the claimed particle size range. One having ordinary skill in the art would have been motivated to do this to obtain an optimal particle size for inhaled steroids.

Therefore, the invention as a whole would have been *prima facie* obvious to one skilled in the art at the time it was made.

Conclusion

No claims are allowed.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1617

/Yong S. Chong/
Primary Examiner, Art Unit 1627